## REMARKS

Claims 13 and 14 currently appear in this application. The Office Action of September 9, 2004, has been carefully studied. These claims define novel and unobvious subject matter under Sections 102 and 103 of 35 U.S.C., and therefore should be allowed. Applicants respectfully request favorable reconsideration, entry of the present amendment, and formal allowance of the claims.

### Claim Objections

Claim 13 is objected to because of typographical errors in step (c).

Accordingly, these self-evident typographical errors have been corrected. Additionally, claim 14 has been corrected so that the verb agrees with the subject.

### Rejections under 35 U.S.C. 112

Claim 13 is rejected under 35 U.S.C. 112, second paragraph, as failing to distinctly claim the subject mater which the applicant regards as his invention.

This rejection is respectfully traversed. Claim 13 has now been amended to provide antecedent basis for "genes", as well as to change "in" to -on—so as to agree with the recitation in step (f) of claim 13.

**Art Rejections**

Claims 13 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang et al. in view of Schena.

This rejection is respectfully traversed. Claims 13 and 14 are directed to a method for determining a signal transduction pathway that is influenced by an endocrine-disrupting activity of a test substance (claim 13) and a method for determining a substance that causes endocrine disruption in a manner similar to an endocrine disruptor (claim 14). Both of the claimed methods are characterized by a common feature, *i.e.*, the use of a DNA array in which the genes on the DNA array comprise at least one gene for each of the respective group (1) to (17). The present invention is based on the finding by the present inventors that the set of genes from groups (1) to (17) are useful for the method claimed herein. This feature of the claimed invention is not disclosed, suggested, or taught by the cited references.

Wang et al. disclose identification of dioxin (TCDD)-responsive genes in Hep G2 cells using differential mRNA display RT-PCR (DD RT-PCR). Specially, Wang et al. use total RNA isolated from human hepatoma Hep G2 cells which had been treated with TCDD and then subjected to DD RT-PCR in which amplified cDNAs were analyzed by electrophoresis on a polyacrylamide-urea gel (see Experimental Procedures on page

785 of Wang et al.). As a result, Wang et al. identified four TCDD-responsive genes. Two of these genes were known genes, while the remaining two were unknown genes (see the paragraph bridging from page 787 to 788 of Wang et al.).

Thus, it is clear that the Wang et al. process obtains information from unknown genes. If information on unknown genes is obtained, one cannot use that information for analyses including determination of a signal transduction pathway or the like. In contrast thereto, using a DNA array wherein the genes on the DNA array comprise at least one "known" gene for each of the respective groups (1) to (17) as defined in claims 13 or 14, one skilled in the art can readily determine a signal transduction pathway or the like according to the claimed method. Thus, there is nothing in Wang et al. that would lead one skilled in the art to the herein claimed invention.

Schena discloses a method for monitoring differential expression of the cognate human genes using a highly sensitive two-color hybridization assay. As examples, heat shock response and phorbol ester signaling are examined. Specifically, microarrays containing many (about 1000, as on page 10614, right column, lines 8-10) human cDNAs were used to examine the heat shock response in control (37°C) and heat-treated (43°C) cells (see page 10615, left column, lines 23-

28) or the cellular effects of phorbol ester treatment (page 10617, left column, lines 9-13). As can be seen from Figure 2 of Schena, the patterns of activated and repressed genes in cells with different treatments are quite different from each other.

If one intended to make the Schena method specialized for determination of a signal transduction pathway that is influenced by an endocrine disrupting activity of a test substance or the like, selection of genes whose expression is influenced by endocrine disruptors would be required. Even if Schena is combined with Wang et al., one may only be able to obtain TCDD-responsive cells using a microarray containing many cDNAs. The thus obtained results do not lead to the herein claimed invention because this procedure can correspond only to a preliminary step for completing the herein claimed method.

The method of the present invention is specialized for determination of a signal transduction pathway that is influenced by an endocrine disrupting activity of a test substance or the like using a DNA array in which the genes on the DNA array comprise at least one gene for each of the respective groups (1) to (17). The genes on the DNA array of the present invention have been carefully selected based on

results obtained by mass screening such as those described in the cited references.

Thus, the claimed invention could not have been obtained by combining Schena with Wang et al., since these references neither disclose, teach, or suggest the use of a DNA array in which the genes on the DNA array comprise at least one gene for each of the respective groups (1) to (17).

Submitted herewith is the declaration of Junichi MINENO, one of the inventors of the present application. This declaration described experiments using a DNA array comprising the carefully selected genes of the present invention. The marks (a) through (q) in the declaration corresponding to (1) to (17) in the claims. The expression patterns and the signal transduction pathways analyzed based on the expression patterns can only be obtained according to the present invention. The expression patterns and signal transduction pathways analyzed based on expression patterns cannot be obtained based on the combination of Wang et al. and Schena because these references provide no disclosure concerning the DNA array comprising the specific set of genes. However, one skilled in the art can readily determine a signal transduction pathway or the like based on the expression patterns and/or the signal transduction pathways obtained according to the method claimed herein.

Entry of this amendment is respectfully requested, as the only amendments to the claims were to correct self-evident typographical errors. No new issues are raised by the present amendment.

In view of the above, it is respectfully submitted that the claims are now in condition for allowance, and favorable action thereon is earnestly solicited.

Respectfully submitted,

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